SAP 20-AVP-786-306

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Product:
AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q])

A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type

Protocol No. 20-AVP-786-306
Protocol Version and Date: 1.2 (29 Apr 2020)
IND No. 124099

Statistical Analysis Plan

Version: 4.0

Date: 03-Sep-2024

CONFIDENTIAL - PROPRIETARY INFORMATION

SAP 20-AVP-786-306

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0	19-Oct-2020	PPD	CCI
2.0	15-Sep-2021		
3.0	01-Nov-2021		
3.1	07-June-2023		
4.0	03-Sep-2024		

SAP 20-AVP-786-306

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
Signature: PPD *Electronically signed by: PPD Reason: I am the author Date: Sep 18, 2024 17:14 EDT* **Email:** PPD	
Authoring Biostatistician PPD Principal Biostatistician	**Date** (dd-Mmm-yyyy)
Signature: PPD *Electronically signed by PPD PPD Reason: I am the approver Date: Sep 18, 2024 16:18 CDT* **Email:** PPD	
Senior Reviewing Biostatistician Busuyi Agbetunsin Principal Biostatistician	**Date** (dd-Mmm-yyyy)
Otsuka Pharmaceutical Development & Commercialization, Inc.	
PPD Biostatistics	**Date** (dd-Mmm-yyyy)

SAP 20-AVP-786-306

Table of Contents

SAP 20-AVP-786-306

SAP 20-AVP-786-306

1 Glossary of Abbreviations

Abbreviation	Description
ºF	Degrees Fahrenheit
ºC	Degrees Celsius
ADWG	Agitation Definition Working Group
AAD	Agitation in Alzheimer's Dementia
ADAMS	Aging, Demographics, and Memory Study
AE	Adverse Event
ANCOVA	Analysis of Covariance
AVP-786	d6-DM and Q
BP	Blood Pressure
bpm	Beats per Minute
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CGIS-Agitation	Clinical Global Impression of Severity of Illness scale for Agitation
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central Nervous System
COVID-19	Coronavirus Disease-2019
CYP	Cytochrome P450
d6-DM	Deudextromethorphan Hydrobromide (or Deudextromethorphan)
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
HbA1c	Glycosylated Hemoglobin
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intent-to-Treat
IRB	Institutional Review Board

SAP 20-AVP-786-306

Abbreviation	Description
IWRS	Interactive Web-Response System
mADCS-CGIC-Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale for Agitation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMSE	Mini Mental State Examination
NIA-AA	National Institute on Aging - Alzheimer's Association
NPI	Neuropsychiatric Inventory
NPI-AA	Neuropsychiatric Inventory Agitation/Aggression
NPI-NH	Neuropsychiatric Inventory – Nursing Home
OTC	Over-the-Counter
PCR	Potential Clinical Relevance
PH	Potential Hydrogen
PK	Pharmacokinetic
PT	Preferred Term
Q	Quinidine Sulfate
QOL	Quality of Life
QRS	Total Time of Ventricular Depolarisation. It is measured from the beginning of the Q or R wave until the end of the S wave
QT	Total Time of the Electrical Ventricular Systole, that is, the set of Ventricular Depolarisation and Repolarisation
QTc	Corrected QT Interval
QTcF	QTc by Fridericia's Formula
RUD-Lite	Resource Utilization in Dementia-Lite
S-STS	Sheehan Suicidality Tracking Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SPCD	Sequential Parallel Comparison Design
SSRI	Selective Serotonin Reuptake Inhibitors
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid-Stimulating Hormone

SAP 20-AVP-786-306

Abbreviation	Description
TUG	Timed Up and Go
ULN	Upper Limit of Normal
US	United States

SAP 20-AVP-786-306

2 Introduction

Alzheimer's disease, the most common form of dementia, is a progressive neurodegenerative disease that eventually leads to death. There are an estimated 5.8 million people in the United States (US) with Alzheimer's dementia and this number is expected to reach 14 million by the year 2050[1]. National estimates of the prevalence of all dementias from population-based studies including the Aging, Demographics, and Memory Study (ADAMS), a nationally representative sample of older adults, show that 14 percent of people age 71 and older in the US have dementia[2,3].

Agitation is widely recognized by clinicians as a common and important clinical feature of Alzheimer's disease and other forms of dementia[4,5,6,7,8]. Agitation, aggression, depression, hallucinations, and delusions are estimated to affect up to approximately 90% of patients with Alzheimer's disease with an increase in prevalence as the disease progresses[4,9]. In a meta analyses of data from 55 studies, overall prevalence of agitation ranged from 5% to 88% across all studies, with 23 studies reporting the prevalence of at least one neuropsychiatric syndrome with a range of 40% to 100%. Agitation in patients with dementia is associated with increased functional disability, worse quality of life[10,11,12], earlier institutionalization[13], increased caregiver burden[14,5,15,16,17,18], increased healthcare costs[19,20,13,21], shorter time to severe dementia[22,23], and accelerated mortality[23,24]. Currently, there is no approved treatment in the US to manage agitation in patients with Alzheimer's disease[25]. Pharmacologic treatments for patients with agitation in Alzheimer's disease include off-label use of atypical antipsychotics, selective serotonin reuptake inhibitors, benzodiazepines, and anticonvulsants[26,27,28]; however, these treatments provide only modest efficacy that is offset by relatively poor adherence, safety, and tolerability[29,30]. It is widely recognized that a safe and effective treatment for patients with agitation in Alzheimer's disease represents a significant unmet need[31]. Such a treatment could profoundly impact patient care, potentially reduce caregiver burden, and improve overall disease prognosis.

AVP-786 is a combination product of deudextromethorphan hydrobromide (d6-DM), a central nervous system (CNS)-active agent, and quinidine sulfate (Q), used as an inhibitor of d6-DM metabolism via the cytochrome P450 (CYP) liver isoenzyme 2D6 (CYP2D6). AVP-786 is being developed by Otsuka Pharmaceutical Development & Commercialization, Inc. for the treatment of neuropsychiatric conditions.

On May 22, 2024, the ODPC management team decided to terminate the development of the AVP-786 compound. Due to this decision, the plan is to now provide only an

SAP 20-AVP-786-306

abbreviated Clinical Study Report (CSR) containing information about baseline characteristics, and safety analyses for the study. The Statistical Analysis Plan (SAP) is being amended to describe only the outcomes planned for analysis in the abbreviated CSR.

3 Trial Objectives

3.1 Primary Objective

The primary objective is to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the treatment of agitation in patients with dementia of the Alzheimer's type.

3.2 Secondary Objectives

The secondary objectives are to:

- Evaluate the effects of AVP-786 compared to placebo on global assessments of severity and improvement of agitation
- Evaluate the effects of AVP-786 compared to placebo on neuropsychiatric symptoms
- Evaluate the effects of AVP-786 compared to placebo on measures of quality of life and resource utilization

SAP 20-AVP-786-306

4 Trial Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) and AVP-786-42.63 (d6-DM 42.63 mg/Q 4.9 mg) compared to placebo for the treatment of agitation in patients with dementia of the Alzheimer's type.

The study consists of a 4-week Screening period, a 12-week double-blind treatment period, and a 30-day Follow-up period. Approximately 750 subjects with agitation of the Alzheimer's type will be enrolled at approximately 110 sites including the US and Europe.

4.1 Screening Period (Day -28 to Day -1)

Subject eligibility will be determined during the Screening visit, which will occur within 4 weeks of the Baseline visit. A protocol eligibility form will be completed for each subject and reviewed by a Medical Monitor for approval prior to participation in the study.

4.2 Double-blind, Treatment Period (12 Weeks)

Patients who are deemed eligible for study participation will enter into the 12-week Double-blind Treatment Period.

The 12-week Double-blind Treatment period consists of

- Blinded Period A (Days 1 to 7): 1-week Double-blind Placebo Lead-in Period and
- Blinded Period B (Days 8 to 85): 11-week Double-blind Randomization Period.

Patients will attend visits at Baseline (Day 1), Weeks 1 (Day 8), 2 (Day 15), 4 (Day 29), 6 (Day 43), 8 (Day 57), 10 (Day 71), and 12/Early Termination (ET; Day 85) during the 12-week Double-blind Treatment Period.

Blinded Period A – *1-week Double-blind Placebo Lead-In Period*

At the Baseline visit (Day 1), all subjects will be enrolled into a 1-week Double-blind Placebo Lead-in Period (Period A).

Blinded Period B – *11-week Double-blind Randomization Period*

At the Week 1 visit (Day 8), subjects will be assessed for placebo response, which is defined as a ≥ 30% improvement on the Cohen-Mansfield Agitation Inventory (CMAI) total score at Day 8 compared to Day 1.

All subjects will be randomized to receive study treatment (AVP-786 or placebo) during the 11-week Double-blind Randomization Period (Period B) regardless of their response to placebo during Period A. Placebo responders, as defined above, will be randomized, and

will participate in the study to maintain blinding and to allow for collection of additional safety data but will be excluded from all efficacy analyses.

Stratification criteria:

Randomization will be stratified by site, baseline concomitant antipsychotic use (yes/no), and placebo response status (placebo responder; placebo non-responder). Study drug will be administered twice daily (BID; morning and evening) starting from the Baseline visit (Day 1) through Visit 8 (Day 85).

Randomization:

At the Week 1 visit, all subjects will be randomized in a 1:1:1 ratio to one of the following double-blind treatment regimens:

- AVP-786-18, or
- AVP-786-42.63, or
- Placebo

Subjects will receive 11 weeks of their assigned treatment regimen.

Blinded – *End of the Efficacy Period*

The term 'end of the efficacy period' used in the protocol refers to the Week 10 visit in the study and will be the time point at which the efficacy outcome measures (CMAI, Clinical Global Impression of Change for Agitation [CGIC-Agitation]), Clinical Global Impression of Severity of Illness for Agitation [CGIS-Agitation], Neuropsychiatric Inventory [NPI]) will be assessed in the analysis. At the Week 10 visit, subjects will have been treated with 9 weeks of double-blind, randomized study medication.

Week 12/Early Termination Visit

The end of the 12-week Double-blind Treatment Period is the Week 12/ET visit. The EuroQol 5-Dimension 5-Level (EQ-5D-5L) and Resource Utilization in Dementia-Lite (RUD-Lite), as well as safety outcome measures, will be assessed at the Week 12/ET visit.

4.3 Follow-up Period

All enrolled subjects, whether they complete the study or terminate from the study early for any reason, will have a Follow-up visit 30 days after the last dose of study drug for select efficacy and safety assessments.

SAP 20-AVP-786-306

4.4 Assessments and Visits

Subjects will attend clinic visits at Screening (Day -28 to -1), Baseline (Day 1), Visit 2 (Week 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7 (Week 10), Visit 8 (Week 12/ET), and 30 days after the last dose of study drug (Follow-up visit).

Study assessments and procedures will be performed at each visit as outlined in the Schedule of Assessments and Visits (Table 1). The primary efficacy measure is the CMAI. Secondary efficacy measures include CGIS-Agitation, CGIC-Agitation, Neuropsychiatric Inventory Agitation/Aggression (NPI-AA), NPI total, EQ-5D-5L, and RUD-Lite.

Pharmacokinetic (PK) measurements of plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be measured from blood samples collected at Visit 2 (Week 1), Visit 5 (Week 6), and Visit 7 (Week 10). PK measurements of urine concentrations of d6-DM and its metabolite d3-DX will be measured from a urine sample collected at Visit 2 (Week 1).

The safety and tolerability of AVP-786 will be assessed by reported AEs, physical and neurological examination, vital signs, clinical laboratory measures, resting 12-lead electrocardiograms (ECG), and the following safety scales: Mini-Mental State Examination (MMSE), Epworth Sleepiness Scale (ESS), and Sheehan Suicidality Tracking Scale (S-STS).

SAP 20-AVP-786-306

Table 1: Schedule of Assessments and Visits

			12-WEEK DOUBLE-BLIND TREATMENT PERIOD								
	Visit:	**Screening[a]**	**Baseline**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 (or ET)**	**Follow-up Visit[b]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8 (±3days)**	**Day 15 (±3Days)**	**Day 29 (±3Days)**	**Day 43 (±3Days)**	**Day 57 (±3Days)**	**Day 71 (±3Days)**	**Day 85 (±3Days)**	**30 (+7) days Post Last Dose**
Procedure	**End of Study Week:**			**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
ELIGIBILITY and HISTORY											
Signed informed consent forms		X									
Inclusion and exclusion criteria		X	X								
Medical, psychiatric, and neurological history		X									
Risk assessment for falls (worksheet and TUG)		X									
Hachinski Ischemic Scale (Rosen Modification)		X									
Protocol eligibility form[c]		X									
EFFICACY											
CMAI		X	X	X	X	X	X	X	X	X	X
CGIS-Agitation		X	X	X	X	X	X	X	X	X	X
CGIC-Agitation				X	X	X	X	X	X	X	
NPI[d]		X[d]	X	X	X[d]	X[d]	X	X[d]	X	X	
EQ-5D-5L			X							X	
RUD-Lite			X							X	
SAFETY											
Vital Signs		X	X	X	X	X	X	X	X	X	
Weight and height[e]			X[e]							X[e]	
Physical and neurological examination		X								X	
ECG		X[f]	X[g]	X[g]			X[h]			X[h]	
Chemistry, hematology, urinalysis		X[i]					X			X[i]	
Urine pregnancy test[j]		X	X							X	

			12-WEEK DOUBLE-BLIND TREATMENT PERIOD								
	Visit:	Screening[a]	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 (or ET)	Follow-up Visit[b]
	Study Day:	Day -28 to -1	Day 1	Day 8 (±3days)	Day 15 (±3Days)	Day 29 (±3Days)	Day 43 (±3Days)	Day 57 (±3Days)	Day 71 (±3Days)	Day 85 (±3Days)	30 (+7) days Post Last Dose
Procedure	End of Study Week:			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	
Adverse events			X	X	X	X	X	X	X	X	X
Prior and concomitant medications, non-drug therapies, nonpharmacological interventions for agitation		X	X	X	X	X	X	X	X	X	X
MMSE		X	X							X	
ESS[k]			X							X	
S-STS		X	X							X	
OTHER PROCEDURES											
PK blood sample[l]				X			X		X		
PK urine sample[m]				X							
CYP2D6 blood sample				X							
Amyloid β blood sample				X							
Administer morning dose of study drug in clinic			X	X			X				
Dispense blister card and diary cards			X	X	X	X	X	X	X		
Review blister card and diary cards				X	X	X	X	X	X	X	

AE = adverse event; CGIC-Agitation = Clinical Global Impression of Change for Agitation; CGIS-Agitation = Clinical Global Impression of Severity of Illness for Agitation; CMAI = Cohen-Mansfield Agitation Inventory; ECG = electrocardiogram; EQ-5D-5L= EuroQol 5-Dimension 5-Level; ESS = Epworth Sleepiness Scale; ET = early termination; MMSE = Mini Mental State Examination; NPI = Neuropsychiatric Inventory; PK= Pharmacokinetics; RUD-Lite = Resource Utilization in Dementia-Lite; S-STS = Sheehan Suicidality Tracking Scale; TUG= Timed Up and Go

a The Screening period may be extended after discussion with and approval by a Medical Monitor.

b All enrolled subjects will have an in-clinic Follow-up visit 30 (+7) days after last dose of study drug for selected safety and efficacy assessments.

c For each subject, a protocol eligibility form will be completed by the site and reviewed by a Medical Monitor for approval prior to participation in the study.

d Only the Agitation/Aggression domain of the NPI will be performed at Screening, and at Visit 3, Visit 4, and Visit 6 (i.e., Days 15, 29, and 57).

e Height and weight will be measured at Baseline (Day 1); only weight will be measured at Visit 8 (Day 85/ET).

f At Screening, 3 ECGs will be performed (e.g., one after the other).

g ECG will be performed predose and 1 to 1.5 hours postdose at Baseline (Day 1) and Visit 2 (Day 8).

h ECG will be performed at any time at Visit 5 (Day 43) and Visit 8 (Day 85/ET).

i Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) will be performed at Screening. Glycosylated hemoglobin (HbA1c) test will be performed at Screening and Visit 8 (Day 85/ET).

j Urine pregnancy test will be performed for women of childbearing potential only.

SAP 20-AVP-786-306

k ESS will be rated only by subjects who have a MMSE score of ≥ 10 at Baseline.
l At Visit 2 (Day 8), the PK blood sample will be collected 1 to 4 hours postdose. At Visit 5 (Day 43), the PK blood sample will be collected predose. At Visit 7 (Day 71), the PK blood sample will be collected at any time. The time of the last 2 doses of study drug prior to collection of the PK blood sample will be recorded in the clinical database.
m At Visit 2 (Day 8), the PK urine sample will be collected 1 to 4 hours postdose.

SAP 20-AVP-786-306

5 Sample Size and Power Justification

The initial sample size is calculated based on the treatment effect of 5.0 points with a standard deviation (SD) of 16.5 in the change from the end of Period A (Week 1 visit) to the Week 10 visit (9 weeks of treatment with double-blind, randomized study medication) in the CMAI total score, to achieve 85% power at a 2-sided alpha level of 0.05. The resulting sample size is approximately 600 evaluable subjects randomized in a 1:1:1 ratio to AVP-786-18, AVP-786-42.63, or placebo to explore the efficacy, safety, and tolerability of AVP-786-18 and AVP-786-42.63 versus placebo. In order to have 600 evaluable subjects in the mITT Population (defined in Section 6.1), and further adjusting for a 20% non-evaluability due to placebo responders/dropout impact, a total of 750 subjects will be randomized.

The statistical assumption of the treatment effect of 5.0 points is based on post-hoc analyses of data obtained from the completed AVP-786 Phase 3 studies. Due to the limitations of applying assumptions based on the post-hoc analyses, an unblinded interim analysis will be conducted by a Data Monitoring Committee (DMC) to insure adequate sample size and power for the study. The final sample size could be increased as per recommendation of the DMC.

SAP 20-AVP-786-306

6 Statistical Methods

6.1 Analysis Populations

The following analysis populations are defined for this study:

Enrolled Population: consists of all subjects enrolled in the Double Blind Period A of this study.

Randomized Population: consists of all subjects who were randomized in the Double-Blind Period B of this study. Subjects are considered randomized when they are assigned a treatment number by interactive web-response system (IWRS) at the Week 1 visit (Day 8). A subject receiving trial treatment outside of the IWRS will not be considered randomized, but safety will be reported.

Safety Population: consists of all subjects who were randomized in the Double-Blind Period B of this study, and take at least one dose of double-blind, randomized study medication. Subjects who are randomized in the Double-blind Period B of this study will be excluded from this population only if there is documented evidence (i.e., drug dispensed = drug returned or no trial drug dispensed) that the subject did not take study drug. If a subject is dispensed trial medication and is lost to follow-up, he/she will be considered to have been exposed. Subjects will be analyzed according to treatment received. In the event a subject receives more than one treatment, the subject will be summarized by the treatment received most frequently.

Intent-to-Treat (ITT) Population: consists of all subjects in the Randomized Population, who took at least one dose of double-blind study medication and have an end of Period A (Week 1 visit) CMAI total score and at least one post-treatment Period B CMAI total score. Subjects will be analyzed according to their randomized treatment assignment.

The ITT population will not be used for the abbreviated CSR.

Modified Intent-to-Treat (mITT) Population: The mITT population will be the primary analysis population for efficacy analyses. The mITT population consists of all subjects who are in the ITT population and are placebo non-responders. Placebo non-responders are defined as subjects who have a < 30% improvement (in terms of reduction) on the CMAI total score during Period A evaluated at the Week 1 visit (Day 8) compared to the Baseline visit (Day 1). Subjects will be analyzed according to their randomized treatment assignment.

The mITT population will not be used for the abbreviated CSR.

SAP 20-AVP-786-306

6.2 Primary Estimand

The statement defining the primary estimand given in previously approved versions of the SAP is no longer applicable.

6.3 Primary Analysis Method

The primary analysis method previously defined in earlier versions of the SAP is no longer applicable.

6.4 Handling of Missing Data

6.4.1 Medication Dates

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only. Imputed dates will not be presented in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of Week 1 visit (Day 8) date, then the day of the Week 1 visit date will be imputed. Otherwise, the first of the month will be used.
- If day and month are missing and the year matches the year of the Week 1 visit date, then the month and the day of the Week 1 visit date will be imputed. Otherwise, January will be used.
- If the start date is completely missing, the start date will not be imputed. If the stop date is after Week 1 visit date, then the medication will be both prior and concomitant. If the stop date is prior to the Week 1 visit date, then the medication will be a prior medication only.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- For stop dates, if the day is missing, then the last day of the month will be used.
- If the month is missing, then December will be used.
- If the stop date is completely missing then the date of last study visit will be used.
- If an imputed stop date is after the date of last study visit, then the date of last study visit will be used.

6.4.2 Adverse Events

For adverse events (AE) with incomplete dates, the following rules will be used to impute start dates for the sole purpose of determining if an AE is treatment-emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the Week 1 visit date, the day of the Week 1 visit date will be imputed and the AE will be considered treatment-emergent. Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the Week 1 visit date.
- If the day and month are missing, and the year matches the year of the Week 1 visit date, then the month and the day of the Week 1 visit date will be imputed, and the AE will be considered treatment-emergent. Otherwise, January will be used and the treatment-emergent status will be assessed relative to the Week 1 visit date.
- If the start date is completely missing, then the AE will be considered treatment-emergent unless the stop date is complete and prior to the Week 1 visit date or provides enough partial information to rule out a treatment-emergent status.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date and the treatment-emergent status will be assessed relative to the Week 1 visit date.

7 Study Conduct

7.1 Subject Disposition and Analysis Population

A summary of subject disposition will be provided including the number of subjects screened, signer of informed consent, number of screen failures, and reason for screen failure. In addition, the number and percent of subjects in each of the following categories will be provided:

- Number of subjects enrolled in Period A
- Number of subjects randomized in Period B
- Signer of informed consent among randomized subjects in Period B
- Subjects randomized who did not receive study medication
- Completed the study

- Discontinued early from the study
- Reasons for early study discontinuation

A separate summary will be provided for the number of subjects in each analysis population (Enrolled, Randomized, Safety, ITT, and mITT Populations).

7.2 Treatment Compliance

Patients and caregivers will be instructed to return all dispensed study drug, including unused and used empty blister cards, to the clinic on Visits 2 through 8 (Days 8, 15, 29, 43, 57, 71, and 85/ET). For this study, compliance will be defined as when a subject takes at least 80% of their scheduled doses (compliance range 80% to 120%). Caregivers will be provided with diary cards and will be instructed to record daily the number of capsules taken and the time of administration.

Based on the Study Medication panel of the CRF, compliance in taking study medication is calculated by dividing the number of capsules taken by the total number of capsules the subject was scheduled to take during the study period, multiplied by 100. For lost to follow-up subjects, last study medication end date record will be used as the treatment end date.

Treatment compliance will be summarized separately for Period A and Period B, with extent of exposure in the same table for the Safety Population.

7.3 Protocol Deviation

Major or important protocol deviations will be summarized by study site and type of deviation for randomized subjects by treatment group.

8 Baseline Characteristics

8.1 Study Baseline Definition

For analysis of double-blind Period B data, Baseline is defined as the last available measurement prior to the first dose of double-blind, randomized study medication, scheduled at the Week 1 visit (Day 8).

The first dose of double-blind Period B data will be based on the following sources:

1.) Date of In-Clinic dosing Completed at Visit 2
2.) For subjects who do not have in-clinic dosing recorded at Visit 2, At Home dosing logs will be used. The date of first kit intake from a kit dispensed more than 6 days after the first intake during the Period A will be used as the first dose of double-blind Period B treatment.

8.2 Study Day

The following Study Day definition will be used for the purpose of statistical summary and analysis. For study days on or after the date of double-blind randomized treatment start, Study Day will be calculated as assessment date – first dose date in Period B + 1. For study days prior to Period B dosing, Study Day will be calculated as assessment date - first dose date in Period B. Further, there will be no Study Day 0.

8.3 Demographic Characteristics

Baseline demographic characteristics including age, gender, race, ethnicity, height, and weight will be tabulated by treatment group for the Randomized Population. Additional summaries by the following subgroups will be also generated: by gender, by age group (< 65; ≥ 65), by race, and by region. Subject characteristics such as signer of informed consent, living arrangements, and caregiver relationship to subject will be summarized.

Mean, range and standard deviation will be used to describe continuous variables such as age. Frequency distributions will be tabulated for categorical variables such as race.

8.4 Medical History

Medical history information will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. A summary of medical, psychiatric, neurological (excluding Alzheimer's), and Alzheimer's disease history will be presented for the Randomized Population (by treatment group and overall). Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT). Medical history will be provided in subject listings.

8.5 Baseline Disease Characteristics

For the Randomized Population, baseline and baseline disease characteristics will be summarized by treatment group and overall. The following baseline characteristics will be summarized at baseline: number (%) of institutionalized / non institutionalized subjects; CMAI total score; CMAI derived agitation factors of aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior; Clinical Global Impression of Severity of Illness-Agitation (CGIS-A) score, Neuropsychiatric Inventory (NPI) total score; Agitation/Aggression domain of the NPI (NPI-AA) score; EQ-5D-5L (subjects with

MMSE score ≥ 10 at baseline visit only), EQ-5D-5L-proxy, MMSE score; Sheehan STS score; and ESS (subjects with MMSE score ≥ 10 at baseline visit only).

Number of subjects with presence of psychotic symptoms will be summarized at baseline using NPI Delusion and Hallucination score. The counts will be provided for the following categories: NPI item score ≥ 4, ≥ 5, ≥ 6 on either hallucination or delusion score.

Tables will be presented by treatment group and overall.

9 Efficacy Analysis

Due to the early termination of the study, efficacy summaries of the primary and secondary efficacy endpoints will not be provided. Descriptive analyses of the RUD are planned.

9.1 Resource Utilization in Dementia (RUD) Lite Analyses

The RUD is administered as a semi-structured interview with the subject's primary caregiver and contains 2 sections; one focusing on caregiver impact (loss of work and leisure time incurred by caregiver) and the other focusing on the subject's use of healthcare resources. The total healthcare costs associated with the subject's dementia can be estimated by multiplying the number of units used (e.g., hours of caregiver time, visits to doctors, nights in accommodation) by the corresponding unit price vector.

The RUD-Lite (RUD 5.0) is a shorter version of the RUD developed to reduce the interview burden on caregivers. Questions related to caregiver resource use (e.g., work status, respite or hospital care, social services, day care, or drug use), which in general is low for caregivers, have been removed from the RUD-Lite. The RUD-Lite will be assessed at Baseline (Day 1) and Visit 8 (Week 12/ET).

Descriptive analyses of the following RUD variables will be provided at baseline and at Week 12/ET:

Institutionalized subjects included in Safety Population:

- Formal caregivers demographic characteristics: age, sex
- Subject living accommodation characteristics: living accommodation, living arrangements, number of subjects with temporary accommodations and type, average nights in temporary accommodations
- Caregiving time:
  - Average time spent assisting the subject each day for items 1a), 2a), and 3a) on the RUD questionnaire

  - Average number of days per month for items 1b), 2b), and 3b) on the RUD questionnaire;
- Healthcare resource use:
  - Number of hospitalizations and type of ward, number of emergency visits, number of health services and type of healthcare professional, and type and duration of services
  - Overall amount of utilization expressed in the appropriate unit (visits/contacts, days) including number of days receiving care
  - Percentage of subjects with at least one utilization
  - Amount of utilization expressed in the appropriate unit (visits/contacts, days) within subjects with at least one utilisation

Non-Institutionalized subjects included in Safety Population:

- Informal caregiver demographic and other characteristics: age, sex, relationship to subject, number of children, cohabitation (Yes/No), number of additional caregivers, level of contribution
- Subject living accommodation characteristics: living accommodation; living arrangements, number of subjects with temporary arrangements and type, average nights in temporary accommodations
- Caregiving time
  - Average time spent assisting the subject each day for items 1a), 2a), and 3a)
  - Average number of days per month for items 1b), 2b), and 3b)
- Aspects of caregiver burden
  - Sleeping hours of the caregiver: average daily sleep time, and the change from baseline on this outcome
  - Caregiver responsibilities affect their work: work (Yes/No) and reasons for No; average number of days missed work due to caregiving, average number of part of a day missed due to caregiving
  - Among the subset of subjects whose caregiver has reported they work for pay at baseline, the following will be summarized:
    - Number of days of work missed completely
    - Number of days of work missed partially or completely
- Subject temporary institutionalization; institutionalisation (identified as the following living accommodations: “dementia-specific residential accommodation” and “long-term institutional care”):
  - Number of subjects reporting at least one institutionalisation
- Subject healthcare resource utilization
  - Number of hospitalizations and type of ward, number of emergency visits, number of health services and type of healthcare professional, and type and duration of services
  - Overall amount of utilization expressed in the appropriate unit (visits/contacts, days) including number of days receiving care

- Percentage of subjects with at least one utilization
- Amount of utilization expressed in the appropriate unit (visits/contacts, days) within subjects with at least one utilisation

10 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, resting 12-lead ECGs, pregnancy tests, and physical and neurological examination. In addition, data from the following safety scales will be evaluated: MMSE, ESS, and S-STS. Prior and concomitant medications as well as exposure to study drug will also be summarized. Prospectively defined criteria will be used to identify potentially clinically relevant (PCR) abnormal values for clinical laboratory tests, vital signs, and ECGs.

Safety analysis will be conducted based on the Safety Population. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of double-blind, randomized study medication at Visit 2 (Week 1), unless specified otherwise.

10.1 Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 27.0). AEs will be summarized and presented on the Safety Population. Summaries will be ordered alphabetically by SOC and then, within a SOC, alphabetically by PT. The incidence of the following events will be summarized by treatment group:

a) Treatment-emergent AEs (TEAE) by SOC and PT
b) TEAEs at least 5% in the combined AVP-786 group and twice greater than placebo
c) TEAEs at least 2% in the combined AVP-786 group and greater than placebo
d) TEAEs by severity
e) Drug-related TEAEs
f) TEAEs with an outcome of death
g) Serious TEAEs
h) Drug-Related Serious TEAEs
i) Non-serious TEAEs
j) TEAEs leading to discontinuation from study drug
k) Drug-related TEAEs leading to discontinuation from study drug
l) AEs of special interest
m) COVID-19 related TEAEs

The following AEs of special interest will be summarized by PT terms only:

1) Fall
2) Syncope
3) Bradycardia (including Bradycardia, Sinus Bradycardia, Central Bradycardia)
4) Rash (including preferred terms containing Rash, Dermatitis, Rash, Dermatitis, Eczema, Miliaria)
5) Thrombocytopenia
6) Serotonin Syndrome

The above summaries will also be prepared for TEAEs potentially causally related to the study drug.

In addition, the subjects with use of beta blockers at baseline will be analyzed for TEAEs. Analysis will be done for subjects taking baseline beta blockers that are and are not major substrates of CYP2D6. Beta blockers that are major CYP2D6 substrates include:

- Carvedilol
- Metoprolol
- Propranolol
- Timolol
- Nebivolol Hydrochloride

All other beta blockers will not be considered major CYP2D6 substrates. For this analysis, TEAEs by SOC and PT will be assessed for those who took baseline beta blockers that are CYP2D6 major substrates and for those who took beta blockers that are not CYP2D6 major substrates.

Treatment-emergent AEs are defined as AEs with an onset date on or after the start of double-blind treatment (Week 1), and within 30 days after last day of double-blind dosing. In more detail, TEAEs are all AEs which started after start of double-blind study drug treatment; or if the event was continuous from baseline and was worsening, serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy. A drug-related event is defined as an event assessed as 'Possibly Related' or 'Related' by the Investigator or where relationship records are missing. AEs occurring up to 30 days after the last day of double-blind dosing will be included in the summary tables.

Additionally, time to onset of common TEAEs will be summarized descriptively. A common TEAE is an AE with an incidence of ≥ 3% of either AVP-786 treatment group and ≥ 2 times the incidence of the Placebo treatment group. Time to onset is calculated as AE start date – first dose date. A value of 0 indicates the AE started on the day of first dose.

Duration of common TEAEs and duration as a percentage of total study day of common TEAEs will be summarized descriptively similarly to time to onset of common TEAE. Also, number of subjects with at least one recurrence of common TEAEs will be

summarized. Duration is defined as AE stop date – AE start date + 1. Duration as a percentage of total study days = duration / (last dose date – first dose date +1)*100. Recurrence is defined as a new report of the same TEAE with a new AE start date within a given treatment.

10.2 Clinical Laboratory Tests

10.2.1 Change from Baseline in Laboratory Tests

Unless otherwise specified, the following clinical laboratory assessments are to be performed at Screening (Day -28 to Day -1), Visit 5 (Week 6), and Visit 8 (Week 12/ET):

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, creatine kinase, gamma-glutamyl transferase, triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
- Urinalysis (pH, specific gravity, protein, glucose, ketones, blood, leucocyte esterase, nitrates, and microscopic appearance)
- Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) at Screening visit only
- Glycosylated hemoglobin (HbA1c) test at the Screening visit and Visit 8 (Week 12/ET) only
- CYP2D6 genotyping at Visit 2 (Week 1) only
- Amyloid β biomarker at Visit 2 (Week 1) only

Summary statistics for mean and mean change from end of Period A (Week 1) in the routine clinical laboratory measurements will be provided by treatment and by visit. Shift tables for chemistry, hematology and urinalysis using categories of low, normal, and high, comparing laboratory test results from end of Period A (Week 1) to end of treatment (EOT) will be presented with percentages based on subjects with a non-missing value at end of Period A (Week 1) and EOT visit. End of Treatment (EOT) is defined as the last assessment, whenever it occurred.

Thyroid function tests, Glycosylated hemoglobin, CYP2D6 genotyping, and Amyloid β biomarker will be provided in listings only.

10.2.2 Potentially Clinically Relevant Values

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria in Appendix 1 for laboratory tests will be summarized by treatment group. A listing of PCRs by subject and by test will be provided.

10.2.3 Potentially Liver Injury Related Laboratory Test

Total bilirubin level will be checked for any subjects with increased ALT or AST levels greater or equal to 3 × the upper limit of normal (ULN) (or baseline).

Liver injury related laboratory test results, for subjects who meet the following criteria, will be summarized:

- AST or ALT ≥ 3 × ULN and
- TBL ≥ 2 × ULN

10.3 Pregnancy Tests

Urine pregnancy tests are to be performed for women of childbearing potential at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Week 12/ET).

Pregnancy test results will be provided in a listing only.

10.4 Physical and Neurological Examination and Vital Signs

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1) and Visit 8 (Week 12/ET). The physical examination will include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination will include assessments of mental status, cranial nerves, motor system, reflexes, coordination, gait and station, and sensory system.

Physical and neurological examination findings will be listed by subject.

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed at all clinic visits, except the Follow-up visit. Supine BP and HR will be measured after a subject has rested for at least 5 minutes in the supine position. Each measurement will be taken twice in the same position and recorded. After the measurement of supine BP and HR, the subject will stand still for up to 3 minutes and a single measurement of standing BP and HR will be recorded within 1 to 3 minutes of standing. Respiratory rate (breaths/minute)

and body temperature (°F/°C) will be assessed at all clinic visits. Height and weight will be measured at Day 1; only weight will be measured at Visit 8 (Week 12/ET).

Summary statistics for change from end of Period A (Week 1) in vital signs, and body weight will be provided by treatment group.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria in **Error! Reference source not found.** for vital signs and body weight will be summarized by treatment group. Listing of PCRs by subject and by test will be provided.

10.5 12-Lead ECG

A resting 12-lead ECG will be performed at Screening, Day 1, Visit 2 (Week 1), Visit 5 (Week 6), and Visit 8 (Week 12/ET). At Screening, 3 ECGs will be performed (e.g., one after the other). At Day 1 and Visit 2 (Week 1), 2 ECGs will be performed, one predose and one postdose 1 to 1.5 hours after study drug dosing. An ECG will be performed at any time at Visit 5 (Week 6) and Visit 8 (Week 12/ET). ECG data will include general findings, heart rate (beats/minute), QRS complex, PR, and QTc intervals (milliseconds).

Summary statistics for change and percent change from end of Period A (Week 1) in ECG parameters will be provided by treatment group and by visit. ECG changes from pre-dose to post-dose will also be summarized by treatment group and by visit.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria in **Error! Reference source not found.** for ECG will be summarized by treatment group. Listing of PCRs by subject and by test will be provided.

For the analysis of QT and QTc, data from 3 consecutive complexes (representing three consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: QTcF=QT/(RR^0.33)

Categorical changes in ECG parameters during the double-blind treatment period will be summarized based on the following criteria:

Categorical Change Criteria in QT/QTc Parameters		
Classification	**Category**	**Criteria**
QT	New Onset (≥ 450 Msec for men or ≥ 470 Msec for women)	New onset in QT means a subject who attains a cut off value during treatment period but not at baseline.

SAP 20-AVP-786-306

Categorical Change Criteria in QT/QTc Parameters		
Classification	**Category**	**Criteria**
QTcF	New Onset (≥ 450 Msec for men or ≥ 470 Msec for women)	New onset in QTc means a subject who attains a cut-off value during treatment period but not at baseline.
	New Onset (≥ 450 Msec for men or ≥ 470 Msec for women) And > 10% Increase	New onset and > 10% increase in QTc means a subject who attains a cut off value and > 10% increase during treatment period but not at baseline
	New Onset (> 500 Msec)	New onset (> 500 msec) in QTc means a subject who attains a value > 500 msec during treatment period but not at baseline.
	Increase 30 - 60 Msec	Increase from baseline value > 30 and ≤ 60 msec in QTc
	Increase > 60 Msec	Increase from baseline value > 60 msec in QTc

10.6 Mini-Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate the subject's cognitive state. The MMSE total score ranges from 0 to 30, with higher scores indicating better cognitive function. The MMSE will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Week 12/ET).

The mean changes from baseline (Day 1) to Week 12/ET (OC) and the last visit in the double-blind treatment period in MMSE will be tabulated and analyzed by treatment group using ANCOVA. The ANCOVA model for the OC dataset will include the baseline item score as covariate and treatment group as main effect. The ANCOVA model for last visit will include the baseline item score as covariate, study site, and treatment group as main effects. The analyses will be performed in the Safety Population.

10.7 Epworth Sleepiness Scale (ESS)

The ESS is an 8-item questionnaire that is used to measure sleepiness by rating the probability of falling asleep on 8 different situations that most people engage in during the day. The questions are rated on a 4-point scale (0 to 3) where 0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, and 3 = high chance of dozing. A total score of 0 to 9 is considered to be normal. The ESS will be assessed at Baseline (Day 1) and Visit 8 (Week 12/ET) for subjects with an MMSE score of ≥ 10 at the Baseline visit.

The mean changes from baseline (Day 1) to Week 12/ET (OC) and the last visit in the double blind treatment period in ESS total score will be tabulated and analyzed similarly

to MMSE. The ANCOVA model for the OC datasets will include the baseline item score as covariate and treatment group as main effect. The ANCOVA model for last visit will include the baseline item score as covariate, study site, and treatment group as main effects. The analyses will be performed in the Safety Population.

10.8 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors. Each item of the S-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). The S-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. The S-STS will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Week 12/ET).

The mean changes from baseline (Day 1) to Week 12/ET (OC) and the last visit in the double-blind treatment period in S-STS will be tabulated and analyzed. The ANCOVA model for the OC dataset will include the baseline item score as covariate and treatment group as main effect. The ANCOVA model for last visit will include the baseline item score as covariate, study site, and treatment group as main effects. The analyses will be performed in the Safety Population. Summary statistics for total score, suicidal ideation subscale score, and suicidal behavior subscale score will also be presented separately.

10.9 Timed Up and Go (TUG) Test

The TUG test measures the time (in seconds) taken for an individual to stand up from a standard armchair, walk 3 meters, turn, walk back to the chair, and sit down. It is a commonly used scale for measuring functional mobility and risk of falls. The TUG test will be performed only at Screening (Day -28 to Day -1) to assess the risk of falls for the purpose of eligibility for the study.

TUG test measures will be provided in a listing only.

10.10 Hachinski Ischemic Scale (Rosen Modification)

The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms[33]. The total score ranges from 0 to 12, with higher scores indicating a greater risk of vascular dementia. The Rosen-modified Hachinski Ischemic Scale will be completed at the Screening visit to assess the risk of vascular dementia and eligibility for the study by the same physician who performs the neurological examination.

Rosen-modified Hachinski Ischemic Scale measures will not be summarized or listed.

10.11 Prior and Concomitant Medications

Prior medications will be presented separately from concomitant medications in summary tables. Concomitant medications will be summarized separately for Period A and Period B. Any medication with a start date prior to the date of Blinded Period A (Day 1) first dose will be considered a prior medication. Any medication that is ongoing or has a stop date on or after the Blinded Period A (Day 1) first dose date will be considered a concomitant medication in Period A. Meanwhile, any medication that is ongoing or has a stop date on or after the Blinded Period B (Week 1) first dose date but prior to 14 days following the last dose of study drug will be considered a concomitant medication in Period B.

Number and proportion of subjects taking concomitant medications prior to study therapy, during the double blind treatment period (Period A and Period B), and after study therapy will be tabulated by drug classification using the WHO drug dictionary (Global B3 March 2024). Summaries will be provided by Anatomical Therapeutic Chemical (ATC) Level 2 term and PT. Medication summaries will be sorted alphabetically by ATC Level 2 and by PT within ATC Level 2. Subjects will be counted only once for each medication class and each preferred drug name.

Additionally, the number and proportion of subjects taking prior medications and concomitant medications for Alzheimer's disease and for agitation will be summarized in separate tables.

10.12 Extent of Exposure

The start date of double-blind study therapy – either of the 2 AVP-786 doses or placebo - in Period A will be the first day of double-blind placebo lead-in (Day 1). Period B start date will be the first day of double-blind randomization (Week 1). The number and percentage of subjects, who receive double-blind study medication, will be presented by week and by treatment group. Each dosing week will be based on the actual week, i.e., Day 1-7 in Week 1, Day 8-14 in Week 2, etc. This summary will be performed separately for Period A and Period B, on the Safety Population.

The duration of exposure will be descriptively summarized separately for Period A and Period B, and by week and treatment group. Duration of exposure in Period A will be calculated as study drug end date (Period A) - study drug start date (Period A) + 1, not including treatment interruptions. Duration of exposure in Period B will be calculated as study drug end date (Period B) - study drug start date (Period B) + 1, not including treatment interruptions.

The mean daily dosage will be summarized separately for Period A and Period B, by week and treatment group using descriptive statistics. The mean daily dosage per subject per week will be determined for each week of the study. This will be calculated by dividing the sum of individual total doses in a week by the number of days in the week interval. The summary will contain for each treatment group the number of subjects receiving double-blind study medication, and the mean and range of the mean daily dose for each week.

10.13 Analysis of Pharmacokinetics

Any pharmacokinetic (PK) samples collected during the study will not be processed. No summarizations or displays of PK data are planned.

10.14 Time to Study Discontinuation

A separate analysis will be provided for time to study discontinuation. Time to study discontinuation will be measured as the days from the first dose date to the discontinuation date recorded on the study completion status CRF page, calculated as:

Study discontinuation date – first dose date + 1

Subjects that did not discontinue during the study period will be censored at their last visit date within the study period. Kaplan-Meier estimates will be provided by treatment group of the 25th percentile, median, and 75th percentile. 95% CIs will be provided for the median. Analyses will be based on the Safety Population.

11 Conventions

11.1 Study Visit Windows

Study visit windows will be used to map visits using study day intervals. This visit window convention applies to tables, listings, and figures for all efficacy scales. This derived study window variable will be named as WEEK and will be footnoted. In listings, only CRF study visits will be listed.

Table below shows classifications for study day intervals in the double-blind period. The variable “target day” is defined using the number of days since the start of double-blind dosing in Period B (Week 1 Visit). The first day of double-blind dosing in Period B is defined as “Study Day 1”. If more than one observation falls within a particular study day interval, then the last observation within that interval is used. Evaluations occurring more

than 3 days after the last double-blind dosing date (Part B) will not be mapped into study visit windows and will be excluded from efficacy analyses.

Study Day and Visit Window for Period B

Week	Target Day a	Study Day Interval a
1	7	2-14
3	21	15-28
5	35	29-42
7	49	43-56
9	63	57-70
11	77	70-80 b
12	77	74-80 b

a Relative to the first day of double-blind study medication in the Part B double-blind treatment period.
b Evaluations occurring more than 3 days after the last dosing date of double-blind study medication in the Part B double-blind treatment period will be excluded from the efficacy analyses.

11.2 Pooling of Small Sites

Summaries are not planned that would utilize pooled sites. This section is no longer applicable.

12 References

1. https://www.alz.org/alzheimers-dementia/facts-figures. 2019.
2. Plassman BL LK Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. Neuroepidemaiology. 2007;29(1-2):125-32.
3. Wilson RS WD Leurgans SE, Evans DA, Hebert LE, Langa KM, et al. Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States. Alzheimers Dement. 2011;7(1):74-9.
4. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry. 2008;23(2):170-7.
5. Fauth EB, Gibbons A. Which behavioral and psychological symptoms of dementia are the most problematic? Variability by prevalence, intensity, distress ratings, and associations with caregiver depressive symptoms. Int J Geriatr Psychiatry. 2014;29(3):263-71.
6. Borsje P, Wetzels RB, Lucassen PL, Pot AM, Koopmans RT. The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review. Int Psychogeriatr. 2015;27(3):385-405.
7. Wetzels RB, Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. Am J Geriatr Psychiatry. 2010;18(12):1054-65.
8. Gauthier S, Lopez OL, Waldemar G, et al. Effects of donepezil on activities of daily living: integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease. Int Psychogeriatr. 2010;22(6):973-83.
9. Anatchkova M, Brooks A, Swett L, et al. Agitation in patients with dementia: a systematic review of epidemiology and association with severity and course. Int Psychogeriatr. 2019;11:1-14.
10. Conde-Sala JL, Turro-Garriga O, Pinan-Hernandez S, et al. Effects of anosognosia and neuropsychiatric symptoms on the quality of life of patients with Alzheimer's disease: a 24-month follow-up study. Int J Geriatr Psychiatry. 2016;31(2):109-19.
11. Laybourne A, Livingston G, Cousins S, et al. Carer coping and resident agitation as predictors of quality of life in care home residents living with dementia: Managing Agitation and Raising Quality of Life (MARQUE) English national care home prospective cohort study. Int J Geriatr Psychiatry. 2019;34(1):106-113.
12. Livingston G, Barber J, Marston L, et al. Prevalence of and associations with agitation in residents with dementia living in care homes: MARQUE cross-sectional study. BJPsych Open. 2017;3(4):171-178.
13. Knapp M, Chua K-C, Broadbent M, et al. Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. BMJ Open. 2016;6(11):e013591.

14. Senanarong V, Jamjumras P, Harmphadungkit K, et al. A counseling intervention for caregivers: effect on neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2004;19(8):781-8.
15. Ismail MS, Dagerman K, Tariot PN, Abbott S, Kavanagh S, Schneider LS. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer's Disease (CATIE-AD): baseline characteristics. Curr Alzheimer Res. 2007;4(3):325-35.
16. Huis In Het Veld J, Verkaik R, van Meijel B, et al. Self-management by family caregivers to manage changes in the behavior and mood of their relative with dementia: an online focus group study. BMC Geriatr. 2016;16:95.
17. de Mauleon A, Soto M, Ousset PJ, Nourhashemi F, Lepage B, Vellas B. Potentially modifiable factors associated with agitation and aggression in Alzheimer's disease: results of the ICTUS study. Int Psychogeriatr. 2019;31(10):1509-1516.
18. Shin H-Y, Chung E-K, Rhee J-A, Yoon J-S, Kim J-M. [Prevalence and related factors of dementia in an urban elderly population using a new screening method]. J Prev Med Public Health. 2005;38(3):351-8.
19. Costa N, Wubker A, De Mauleon A, et al. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. J Am Med Dir Assoc. 2018;19(1):95.e1-95.e10.
20. Yu X, Chen S, Chen X, et al. Clinical management and associated costs for moderate and severe Alzheimer's disease in urban China: a Delphi panel study. Transl Neurodegener. 2015;4:15.
21. Vossius C, Selbaek G, Saltyte Benth J, Wimo A, Bergh S. The use of direct care in nursing home residents: A longitudinal cohort study over 3 years. Int J Geriatr Psychiatry. 2019;34(2):337-351.
22. Zahodne LB, Ornstein K, Cosentino S, Devanand DP, Stern Y. Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. Am J Geriatr Psychiatry. 2015;23(2):130-40.
23. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. Am J Psychiatry. 2015;172(5):460-5.
24. Sampson EL, White N, Lord K, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. Pain. 2015;156(4):675-83.
25. Ahmed M, Malik M, Teselink J, Lanctot KL, Herrmann N. Current Agents in Development for Treating Behavioral and Psychological Symptoms Associated with Dementia. Drugs Aging. 2019;36(7):589-605.
26. Seitz DP, Gill SS, Herrmann N, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. Int Psychogeriatr. 2013;25(2):185-203.
27. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. The Institute of Psychiatry. 2009.

28. McDermott CL, Gruenewald DA. Pharmacologic Management of Agitation in Patients with Dementia. *Curr* Geriatr Rep. 2019;8(1):1-11.
29. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011;306(12):1359-69.
30. Panel A. Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-694.
31. Garay RP, Citrome L, Grossberg GT, Cavero I, Llorca P-M. Investigational drugs for treating agitation in persons with dementia. Expert Opin Investig Drugs. 2016;25(8):973-83.
32. Rabinowitz, J., Davidson, M., de Deyn, P.P., Katz, I.R., Brodaty, H., & Cohen-Mansfield, J. (2005). Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 13 11, 991-8.
33. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980;7(5):486-8.

CCI

CCI

CCI

CCI

CCI

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Otsuka_20-AVP-786-306_SAP_v4_03SEP2024_CLEAN

Document Number: CCI [redacted]

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	17-Sep-2024 12:16:57
	Biostatistics Approval	17-Sep-2024 05:22:29

AVP306SAP_Final

Final Audit Report 2024-09-18

Created:	2024-09-18
By:	PPD
Status:	Signed
Transaction ID:	CBJCHBCAABAAPma1qxtvD99UyomgXD3crFQeQ8j4dujQ

"AVP306SAP_Final" History

Document created by PPD
2024-09-18 - 9:12:11 PM GMT- IP address: PPD

Document emailed to PPD for signature
2024-09-18 - 9:13:24 PM GMT

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2024-09-18 - 9:14:27 PM GMT

Document e-signed by PPD
Signing reason: I am the author
Signature Date: 2024-09-18 - 9:14:29 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2024-09-18 - 9:14:31 PM GMT

Email viewed by PPD
2024-09-18 - 9:16:46 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony.
2024-09-18 - 9:18:00 PM GMT

Document e-signed by PPD
Signing reason: I am the approver
Signature Date: 2024-09-18 - 9:18:01 PM GMT - Time Source: server- IP address: PPD

Agreement completed.
2024-09-18 - 9:18:01 PM GMT

Syneos Health | Powered by Adobe Acrobat Sign